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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,968	11/06/2001	Carlos Miguel Carcagno	1909.0040002	7301

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,968	CARCAGNO ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-13 and 15-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-13 and 15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 10/13/05 has been acknowledged.

Claims 6 and 14 is canceled

Claims 1-5, 7-13 and 15-20 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is **571-273-8300.**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

The applicant's arguments, filed on 10/13/05 filed have been fully considered but are found not persuasive in view of new grounds of rejections below.

Claim Rejections - 35 USC § 103

Claims 1-5, 13 and 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jixian et al (Bull Acad. Mil. Med. Sci. 21(4):244-246, 1997, English translation provided) in view of Koch at al (EP 0513738 A2, 11/19/1992, *English translation provided*).

The instant claims are drawn to a method for obtaining human erythropoietin by culturing mammalian cells, which express recombinant human erythropoietin in a culture medium comprising insulin. The instant claims are further drawn to mammalian cells selected from the group comprising CHO, COS, BHK, Namalwa, and HeLa. The claims are further drawn to the method wherein the culture medium comprises fetal calf-

free media. The claims are further drawn to a culture media consitig of DMEM, HAM12, NaHCO3, sugars, ethanolamine, sodium pyruvate and insulin. In addition the claims are drawn to method for obtaining human erythropoietin by culturing mammalian cells, which express recombinant human erythropoietin in a culture medium comprising insulin, wherein the culture media comprises insulin in the range of 1-20 mg of insulin per liter of culture media.

Jixian et al teaches production of recombinant human erythropoietin (rHuEPO) using CHO cells in a serum free media (SFM-p) in the presence of insulin. Regarding claim 1-3 specifically the cited art teaches genetically engineered mammalian cells (CHO cells), which express recombinant human erythropoietin (page 2, para. 1.1). Regarding claim 6 the cited art teaches culturing of rHuEPO producing cells in a fetal calf serum-free media designated as SFM-p (page 2; page 4, para. 2.1; page 5 para. 2.2, table-3). The cited art further teaches that the SFM-p comprises various additives which include Se, Ethanolamine, vitamins, peptone, insulin, transferin and some cytokines added in DMEM and F12 medium (abstract, page 2, para. 1.2). Furthermore NaHCO3, sugars and pyruvate are the ingredients found in DMEM and F12 medium (see list of ingredients). In addition the cited art teaches that SFM-p promotes growth and proliferation of rHuEPO expressing CHO cells, which resulted in the production of rHuEPO in culture media.

Even though Jixian teaches production of recombinant human erythropoietin (rHuEPO) using CHO cells in a serum free media (SFM-p) in the presence of insulin, the reference does not specifically teaches that insulin concentration is in the range of 1-20 mg of insulin per liter of culture media.

Koch et al teaches a serum-free culture medium containing insulin for the cultivation of mammalian cells, especially the genetically engineered CHO cells to produce recombinant erythropoietin (page 1). Regarding claims 4-5, the cited art teaches that the serum-free media contains recombinant insulin in the range of 0.1-20 mg/L (page 2 para. 4-6, page 3 para. 2). The cited art further teaches serum free media that comprises recombinant insulin at the concentration of 5mg/L, which is well with in the range of insulin concentration as claimed (i.e. 1-20mg/L) see page 4 para. 7, table-

1; page 6). The cited art further teaches production of erythropoietin in the culture medium by cultivating genetically engineered CHO (encoding EPO), in a serum free culture media containing insulin (page 3, para.3; page4 para.3; page 6).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the teaching of Jixian by incorporating the SFM-p with insulin in the range of 1-20mg/L in view of Koch. One would have been motivated to do so because incorporation of insulin in the range of 1-20mg/L in serum free media is close to cultivation conditions when serum is used. One would have a reasonable expectation of success to produce rHuEPO in CHO using serum free media containing insulin in the range of 1-20mg/L because the cited prior clearly teaches that CHO cells proliferate and produce recombinant EPO under such conditions (see Koch fig-1). In addition onel would have a reasonable expectation of success in culturing recombinant host cells in a culture media consisting of DMEM, F12 and insulin contaiing media, since the use of serum free conditions has been routine in the art at the time the instant invention was filed. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Response to arguments

The applicant argues that there is no suggestion or motivation in Jixian or Koch to combine the teachings to obtain applicants' invention. The applicant argues that even assuming, *arguendo*, that such a suggestion or motivation to combine the references is present, there would be no expectation of success in generating the claimed invention and all of the claim limitations are not taught or suggested by the references. The applicant argues that Kosh teaches besides insulin there are other substances that can affect the growth of mammalian cells such as transferrin and other iron compounds. The applicant argue that by virtue of consisting language the applicant excludes un-recited elements. The applicant argues that invention as claimed is not obvious in view of Jixian and Koch. However, applicant's argument are found not persuasive. Jixian clearly teaches a culture media comprising DMEM and F12 (1:1) obtained from GIBCO-BRL containing the claimed media components $NaHCO_3$, sugars, ethanolamine sodium pyruvate and various amino acids (see Jixian page 2 sec 1.2 and

GIBO-BRL Product reference Guide Cell Culture media Sec 1.1997-1998). In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law (See MPEP 2144). In instant case it is well settled that routine optimization of serum free culture media as claimed here in is not patentable, even if it results in significant improvements over the prior art. Thus the invention as claimed is *prima facie* obvious in view of combined teaching of cited prior art of record.

Claims 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jixian et al (Bull Acad. Mil. Med. Sci. 21(4):244-246, 1997, English translation provided) and Koch at al (EP 0513738 A2, 11/19/1992, *English translation provided*) as applied to claims 1-5, 13 and 15-20 above, and further in view of Yanagi et al (DNA 8(6):419-427, 1989) and Chiba et al (US 3865801, 1975).

Claims 7-10 are drawn to a method for separating supernatant form cells, concentrating the supernatant approximately 50-150 folds and freezing concentrated product. In addition the instant claims are drawn to a method wherein media is added to cells from which the supernatant is separated and culturing the media fed cells.

As stated above, the combined teaching of Jixian and Koch teaches a method of producing EPO in recombinant CHO cells in serum free-condition media. Even though

concentration and cryopresevation of recombinant proteins has been routine in the art, the combined teaching of cited art does not teach concentrating supernatant obtained from rEPO/CHO cells approximately by 50-150 fold. In addition the cited art does not teach freezing the concentrated product.

Yanagi et al teaches isolation of recombinant human erythropoietin produced by Namalwa cells (abstract). Regarding claim 7(c) and 9-10 the cited art teaches separation of EPO containing supernatant from EPO-producing 2A311 cells. The cited art further teaches concentration of EPO form the cell supernatant. The cited art teaches concentration of 2A311 media from 4 liters to 400 ml using an ultra filtration device. The cited art teaches further concentration of media obtained by ultra filtration using CM Affi-gel Blue column and a hydroxylapatite column. The purified preparation was then further concentrated by ultra-filtration followed by gel-permeation on TSK G3000SW columns (page 420, col.2 para. 4, page 422 table-1). The cited art teaches that such a purification procedures resulted in a purification factor that ranges from 17-5390 folds (page 422, table-1).

Chiba et al teaches a method of storing EPO for prolonged periods of time. Regarding claim 7 (d), the cited art teaches storing purified EPO preparation in the frozen state at -20°C (col. 7, lines 4-12).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Jixian by employing purification strategy to concentrate EPO containing media as taught by Yanagi. One would have been motivated to do so because highly purified preparation of EPO is desirable product for clinical uses. In addition it would have be further obvious to store the purified EPO preparation in a frozen state in view of Chiba, since cyropreserved proteins have increases stability. One would have a reasonable expectation of success in doing so, since purification of recombinant proteins from the host cells and cyropreservation of purified protein was routine in the art at the time of filing. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Response to arguments

The applicant argues that neither Yanagi nor Chiba remedy the deficiencies of Jixian, in that they, alone or in combination, fail to teach the method as claimed. However, applicant's arguments are found not prsuasive because as stated above the combined teaching of Jixian and Koch clearly suggest that the method of producing EPO in recombinant CHO cells in serum free-condition media (as claimed) is obvious to one ordinary skill in the art with a reasonable expectation of success. Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Jixian and Koch by employing purification strategy to concentrate EPO containing media as taught by Yanagi. Therefore the invention as claimed is *prima facie* obvious in view of combined teaching of cited prior art of record.

Claims 7 and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jixian et al (Bull Acad. Mil. Med. Sci. 21(4):244-246, 1997, English translation provided), Koch at al (EP 0513738 A2, 11/19/1992, *English translation provided*) as applied to claims 1-5, 13 and 15-20 above, and Yanagi et al (DNA 8(6):419-427, 1989) and Chiba et al (US 3865801, 1975) as applied to claims 7-10 above and in further in view van Reis et al (US 5490937, 1996).

The instant claims are drawn to the method for obtaining human erythropoietin from a mammalian cell culture by concentrating the separated supernatant containing EPO using tangential filtration system through membranes with a molecular cut-off of about 3,000 Daltons. The claims are further drawn to a method sterile filtering the concentrated product through membranes with pores of diameter of about 0.2 mm.

The teaching of Jixian, Koch, Yanagi and Chiba have been stated above. Even though the combined teaching of cited prior art of record teaches production, concentration and storage of recombinant EPO in serum free conditions using CHO cells the cited art does not teach purification of EPO from culture media via a tangential filtration system and sterile filtration of concentrated product.

van Reis et al teaches a tangential flow filtration process and apparatus for separating species of interest (proteins) from a mixture. Regarding claim 11 the cited art

teaches a tangential filtration system through filtration membranes having a pore size that separate species of interest having molecular weight of about 1 to 1000 kDa. The cited art further teaches that ultra filtration membranes for tangential-flow filtration are available as units of different configuration depending upon the volume of the liquid to be handled and variety of pore sizes. Regarding claim 12, the cited art further teaches filtration through micro porous membranes that has a pore size typically from 0.1 to 10 micrometers, which would inherently sterile the filtered product (col.12 lines 12-34). The cited art further teaches that use of tangential flow filtration system for higher fold purification of species of interest (col.4 lines 47-61).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Jixian, Yanagi and Chiba by employing a purification strategy that involves a tangential filtration system and sterile filtration in view of van Reis. One would have been motivated to use tangential filtration system to accomplish large-scale resolution macromolecular mixtures obtained form cell culture media. One would have a reasonable expectation of success, since isolation of protein via tangential flow filtration process was routine in the protein purification art at the time of filing. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Response to arguments

The applicant argues that Van Reis fails to remedy the deficiency of Jixian in that that it does not alone or in combination with Yanagi or Chiba teach the claimed method. However, applicant's arguments are found not prsuasive because as stated above the combined teaching of Jixian and Koch clearly suggest that the method of producing EPO in recombinant CHO cells in serum free-condition media as claimed is obvious to one ordinary skill in the art with a reasonable expectation of success. Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Jixian, Koch, Yanagi and Chiba by employing a purification strategy that involves a tangential filtration system and sterile filtration in view of van Reis. Therefore the invention as claimed is *prima facie* obvious in view of combined teaching of cited prior art of record.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-13 and 15-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 7-13 of U.S. Patent No. 6,777,205. Although the conflicting claims are not identical, they are not patentably distinct from each other because the invention of US '205 is drawn to a method of producing EPO polypeptide, comprising culturing the host cell (CHO, COS, BHK, Namalwa and HeLa) under conditions such that said polypeptide is expressed and recovered. Given the broadest reasonable interpretation to the culture conditions and recovery the method as claim in the US'205 encompasses the subject matter of claims 1-13, and 15-20 of instant application.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

SUMESH KAUSHAL
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